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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,877	03/23/2005	Peter R Chang	0100024/0532135	8753

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EXAMINER	
CLARK, AMY LYNN	
ART UNIT	**PAPER NUMBER**
1655	

NOTIFICATION DATE	DELIVERY MODE
09/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/528,877	CHANG ET AL.	
	Examiner	Art Unit	
	Amy L. Clark	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-18 in the reply filed on 06/26/2007 is acknowledged.

Claims 1-29 are currently pending.

Claims 19-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/26/2007.

Claims 1-18 are under examination.

Information Disclosure Statement

The information disclosure statement (IDS) was submitted on 07/21/2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Please note that all references with a strike through were not considered by the Examiner because Applicant did not provide an English translation of any part of the reference. Where the Examiner indicated that only the abstract was considered, Applicant provided the Examiner with an English translation of the abstract only.

Drawings

The drawings are objected to because the labeling of Figures 1A-1C is faint. Furthermore, Applicant has not labeled the x- or y-axes of Figures 2a, 2b, 2c, 3a, 3b, or

3c. Therefore, it is difficult to tell what exactly is being measured in these figures. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 2-18 are objected to because of the following informalities: the word "Claim" in line 1 of claims 2-18 should be corrected to read "~~C~~claim". The term "α-L-rhamnosidase" in lines 1 and 2 of claim 17 and line 2 of claim 18 appear to be redundant. First of all, naringinase is synonymous with α-L-rhamnosidase, secondly, naringinase inherently contains α-L-rhamnosidase. Is Applicant intending to claim that

there is additional α-L-rhamnosidase? If so, then Applicant needs to better clarify this, particularly since α-L-rhamnosidase is synonymous with naringinase, so of course the solution contains this enzyme, since it is claimed in claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of claim 1 are rendered uncertain by the phrase "providing a solution having rutin suspended therein at conditions suitable for enzyme incubation" in lines 3 and 4 of claim 1 because it is unclear if Applicant means that the rutin is only suspended in solution when the conditions are suitable for enzyme incubation or if Applicant is intending that rutin is first suspended in solution and that the solution is then adjusted conditions suitable for enzyme incubation. What does Applicant mean by "suitable for enzyme incubation" (lines 3 and 4, and 6 and 7) and "unsuitable for said enzyme incubation" (line 9)? The terms "suitable for enzyme incubation" and "unsuitable for said enzyme incubation" are relative terms which render the claim indefinite. The terms "suitable for enzyme incubation" and "unsuitable for said enzyme incubation" are not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Is Applicant intending to claim that the solution is adjusted to a specific pH and temperature or is the solution a specific solution that is "suitable" or "unsuitable"? The lack of clarity renders the claims indefinite since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired.

Claims 1 and 2 recites the limitation "said enzyme incubation" in line 9 of claim 1 and line 2 of claim 2, claims 1, 5, and 18 recite the limitation "the incubation period" in lines 8 and 12 of claim 1, line 1 of claim 5 and lines 1 and 2 of claim 18, claims 3 and 12 recite the limitation "the relative proportion" in line 1 of claim 3 and line 2 of claim 12, and claim 9 recites the limitation "the terminating conditions of solution" in line 9. There is insufficient antecedent basis for this limitation in the claim.

The metes and bounds of claim 2 are rendered uncertain by the phrase "said composition also contains quercetin as a result of said enzyme incubation" in lines 3 and 4 of claim 1 because it is unclear if Applicant means that the rutin is only suspended in solution when the conditions are suitable for enzyme incubation or if Applicant is intending that rutin is first suspended in solution and that the solution is then adjusted conditions suitable for enzyme incubation. What does Applicant mean by "suitable for enzyme incubation" (lines 3 and 4, and 6 and 7) and "unsuitable for said enzyme incubation" (line 9)? The terms "suitable for enzyme incubation" and "unsuitable for said enzyme incubation" are relative terms which render the claim indefinite. The terms "suitable for enzyme incubation" and "unsuitable for said enzyme

incubation" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Is Applicant intending to claim that the solution is adjusted to a specific pH and temperature or is the solution a specific solution that is "suitable" or "unsuitable"? The lack of clarity renders the claims indefinite since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired.

The metes and bounds of Claims 3, 12 and 16 are rendered uncertain by the phrase "the relative proportion" in line 1 of claim 3 and line 2 of claim 12 and D-Δ-gluconolactone is greated than 1mM" in lines and 1 and 2 of claim 16 because the amounts of the ingredients are not set forth in terms of either 'by weight" or "by volume" amount of the total composition. The lack of clarity renders the claims indefinite since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Washino et al. (N, JP, 09-094077 A, Translation provided herein), in view of Kamiya et al. (U, 'Glycosides and Oligosaccharides in the L-Rhamnose Series Part I. Enzymatic Partial Hydrolysis of Flavonoi-glucosides". Agr. Biol. Chem., Vol. 31, No. 2 (1967) 133-136), Allius et al. (V, 'Water-soluble Flavonol (=3-Hydroxy-2-phenyl-4*H*-1-benzopyran-4-one) Derivatives: Chemical Synthesis, Colouring, and Antioxidant Properties". Helvetica Chemica Acta, Vol. 82 (2000) 428-443), Buchholz et al. (A, US Patent Number: 6,420,142 B1), Smythe et al. (B, US Patent Number 2,950,974), Yun et al. (W, "Purification and Some Properties of a β-Glucosidase from *Trichoderma harzianum* Type C-4". Biosci. Biotechnol. Biochem., Vol. 65, no. 9 (2001) 2028-2032), Gallego et al. (V, "Purification and Characterization of an α-L-rhamnosidase from *Asperigallus terreus* of Interest in Winemaking". Journal of Food Science, Vol. 66, No. 2 (March 2001) 204-209, Abstract only) and http://web.archive.org/web/20000109063420/http://academic.brooklyn.cuny.edu/biology/bio4fv/page/enz_act.htm (U1, "Effect of temperature on enzyme activity").

Washino teaches a method of obtaining an isoquercitin-enriched composition, wherein the isoquercitin-enriched composition is obtained by distributing rutin in 100L water at a temperature of 55 °C, adding narginase (please note that narginase is also known as α-L-rhamnosidase and inherently contains α-L-rhamnosidase, as clearly taught by Kamiya) to provide a solution, wherein the pH of the solution is 7. The solution is held at a temperature of 50 °C for 5 hours, condensed and cooled. Isoquercitrin is then precipitated and the precipitate is then collected by filtration and dried (See abstract and pages 2 and 3, paragraph 010, "Example"). Washino does not expressly teach that rutin is suspended in a solution, however, flavonols, such as rutin, have poor solubility in acidic to neutral aqueous solutions modeling natural medium, as clearly taught by Alluis (See page 428, "Introduction" continued onto page 429). Therefore, based upon the known characteristics of rutin, it would be obvious to suspend rutin in a solution taught by Washino, since it was known at the time the invention was made that rutin is not soluble at the pH taught by Washino and, therefore, rutin would not be completely dissolved.

Washino does not teach that the composition contains quercetin as a result of enzyme incubation, nor does Washino teach that the proportion of isoquercitrin in the composition is controlled by adjusting the duration of the incubation period, nor does Washino teach that the relative proportion of quercetin and isoquercitrin is controlled by adjusting the duration of the incubation period. However, at the time the invention was made, a method for enzymatically splitting rutinosides to provide rhamnose and/or corresponding glucopyranosides, such as rutin, isoquercetin and quercetin, comprising

the steps of combining citric acid monohydrated and water, adjusting the pH to 6.6 or 5, adding rutin and nainginase and stirring the reaction mixture at 40 °C for either 24 hours, 21 hours or 46 hours or at a temperature of 36 °C for a period of 24 hours then a further 7 hours, then heating to a temperature of 40 °C for a period of 22 hours and cooling to 15 °C, which reads on a method of producing an isoquercitrin-enriched composition, was known, as was that upon completion of the reaction, the solvent is distilled of under reduced pressure, the glucopyranoside crystallizes out, which can contain small amounts of rutinoside and its aglycone, and is separated from the remaining reaction mixture by suction filtration or filtration or centrifugation, as was that the solid is washed with water and dried to provide rutin, isoquercetin and quercetin in varying amounts, which are dependent upon the reaction conditions (See column 7 and 8 for the examples, which teach the method of enzymatic conversion under "Example 1", "Example 2", Example 3" and "Comparison Example" and see column 6, lines 7-19 for the work-up of the reaction mixture to provide rutin, isoquercetin and quercetin), as clearly taught by Buchholz.

Washino does not teach adding a β-D-glucosidase, such as glucolactone, nor does Washino teach that β-D-glucosidase inhibitor is added before adding an enzyme preparation comprising naringinase to the solution, nor does Washino teach a specific amount of β-D-glucosidase inhibitor. However, Smythe teaches a method of enzymatically converting naringin comprising dissolving two grams of naringin in hot water, adding 10 grams of gluconolactone and 6 grams of citric acid, adjusting the pH to 4, bringing the volume of the solution to a liter and adding 5 grams of naringinase

enzyme. Smythe further teaches maintaining the temperature at 50 °C for two hours to provide complete conversion of naringin to prunin and that the solution is then concentrated under vacuum to provide precipitated prunin (See column 11, "Example 9"). Furthermore, Kamiya teaches that naringinase is composed of β-D-glucosidase and α-L-rhamnosidase and that heating the crude enzyme solution to 60 °C at a pH of 6.4-6.8 inactivates β-D-glucosidase, however, under these conditions, α-L-rhanosidase is very stable and that nariginase is able to convert rutin to isoquercitrin and naringin to prunin (See page 133, abstract and "Introduction"). Please note that β-D-glucosidase catalyzes the hydrolysis of the β-glucosidic linkages of aryl and alkyl β-glycosides and several other oligosaccharides with the release of glucose (See Yun et al., page 2028, Introduction). Kamiya further teaches adjusting the pH to provide different amounts of enzymatic activity of both β-D-glucosidase and α-L-rhamnosidase (See page 134, "The Change of Naiginase Activity by heating at 60 °C and various pH and figure 1). Kamiya further teaches complete conversion of narigin to prunin by a solution of nariginase with acid upon deactivating β-D-glucosidase (See page 134 "Prunin from Naringin", continued onto page 135) and complete conversion of isoquercitrin from rutin by a solution of nariginase with acid upon deactivating β-D-glucosidase (See page 135, "Isoquercitrin from Rutin").

Washino does not teach terminating the enzymatic conversion of rutin to isoquercitrin and quercetin by raising the temperature of the solution to 80 °C to denature the enzyme α-L-rhamnosidase. However, Gallego teaches that the optimum pH and temperature for α-L-rhamnosidase (which is a synonym for nariginase) is 4 and

44 °C, respectively. Please further note that enzyme activity is temperature and pH dependent and that the temperature optimum of every enzyme is different and that after the optimum temperature of the enzyme is reached, the activity rapidly decreases (See http://web.archive.org/web/20000109063420/http://academic.brooklyn.cuny.edu/biology/bio4fv/page/enz_act.htm).

Therefore, it would have been it would have been obvious to one of ordinary skill in the art and one would have been motivated and had a reasonable expectation of success to modify the method taught by Washino to provide the instantly claimed invention by adjusting the duration of the incubation period to provide the desired amount of each ingredient, since the effect of adjusting the duration and conditions of the incubation period were known at the time in the art to effect the amounts of isoquercitrin and quercetin, as clearly taught by Buchholz, as was to add an additional inhibitor of β-D-glucosidase to completely convert rutin to isoquercitrin and quercetin, as clearly taught by Smythe and Kamiya as was to terminate the enzymatic conversion of rutin to isoquercitrin and quercetin by raising the temperature of the solution to denature an enzyme, such as α-L-rhamnosidase, as clearly taught by Gallego and http://web.archive.org/web/20000109063420/http://academic.brooklyn.cuny.edu/biology/bio4fv/page/enz_act.htm.

Furthermore, the result-effective adjustment of particular conventional working conditions (e.g., adjusting incubation conditions to convert a substrate to a product, heating an enzyme to a temperature high enough to denature the enzyme to stop the activity of the enzyme and to add ingredients to the buffer solution to help increase the

amount of substrate converted into a product and the rate of the conversion) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

* Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Should you receive inquiries about the use of the Office's PAIR system, applicants may be referred to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy L. Clark whose telephone number is (571) 272-1310. The examiner can normally be reached on 8:30am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy L. Clark
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August 29, 2007

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